Opioid Treatment and Recovery Through a Safe Pain Management Program

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SPECIFIC AIMS

Opioid prescription drug abuse has become a major public health concern in the United States with mortality rates from fatal overdoses exceeding those from cocaine and heroin.(1) This epidemic coincides with national efforts to improve identification and management of chronic non-cancer pain and associated disabilities.(2, 3) The net result, however, has been ever-growing increases in medical expenditures for chronic pain management related to prescription costs and increased healthcare service utilization among opioid abusers.(4, 5) Healthcare provider prescribing pattern, especially among non-pain management specialists such as primary care, is a major contributor to this public health crisis.(6, 7) *Louisiana, as a major contributor to the epidemic with the nation's 7th highest rate of opioid prescriptions*, has great potential for leading changes in the way we deliver care for patients with chronic non-cancer pain.

We are overdue for implementing safe opioid management strategies in primary care to combat the opioid crisis. Safe opioid management programming requires tackling the complex array of multi-level factors (patient, provider, healthcare system; health policy) that increase risks for misuse, abuse, overdose and mortality. Recent evidence-based practice guidelines provide recommendations on what to do for safe prescribing of opioids (e.g. monitoring risk factors) (7-10), but they do not provide guidance on how to translate them into practice. We must find ways to accelerate practice guideline adoption in primary care in the face of an overdose crisis. Given the high prevalence of psychiatric disorders among patients with chronic non-cancer pain (11-13), care team expansion with integration of collaborative mental/behavioral health services may be the solution. Collaborative care can extend opioid management beyond standardized monitoring of risk factors for opioid misuse or abuse and set clear protocols for next steps in management.

Our *main goal* is to address these critical knowledge gaps from the perspective of primary care transformation in a complex patient population and provide evidence through a *four-year stepped wedge cluster randomized control trial of a multi-component opioid management intervention*. Ochsner Health System, the largest nonprofit, multi-specialty, healthcare delivery system in Louisiana with 35 Accountable Care Network-affiliated primary care clinics, is uniquely poised to identify important considerations for primary care redesign in other areas across the country. The **study aims** are as follows:

- **Specific Aim 1**: To compare the *clinical effectiveness* of EMR-based clinical decision support (EMR CDS) guided care versus additional integrated, stepped collaborative care for opioid management of primary care patients with chronic non-cancer pain (community health worker for care coordination and care management; licensed clinical social worker for cognitive behavioral therapy; clinical pharmacist for medication management). ***Hypothesis 1:*** A higher proportion of patients who receive additional integrated stepped collaborative care management (CCM) compared to EMR CDS guided care only will have greater decreases in total dosage of opioid medication prescribed; and receive guideline concordant care.
- **Specific Aim 2:** To conduct a *cost-effectiveness analysis* comparing EMR CDS guided care versus additional integrated stepped CCM for opioid management of non-cancer chronic pain. ***Hypothesis 2***: Patients who participate in integrated stepped CCM will receive more cost-effective care compared to patients who only receive EMR CDS guided care; and have greater reductions in inpatient hospitalizations and/or emergency department utilization.
- **Specific Aim 3**: To examine *facilitators and barriers to implementing* the multi-component intervention using the Consolidated Framework for Implementation Research. ***Hypothesis 3***: Intervention adaptability to local contexts, clinic readiness for implementation (leadership engagement; available

resources; care team knowledge about clinical guidelines), and physician champions will influence implementation and subsequent performance of the intervention.

We anticipate that our study results will elucidate the role of technology versus care team optimization in changing provider opioid prescribing behaviors. We further anticipate that results of our study will demonstrate that integrated mental/behavioral health care for opioid management of chronic non-cancer pain increases value-based care and leads to greater efficiencies in the way that care is delivered.

RESEARCH PLAN

A. Significance

A.1 Impact of Chronic Opioids on Individual and Populations: Chronic pain affects over 100 million adults in the United States, and approximately 20% of outpatient visits are for non-malignant pain.(3) Efforts to improve identification and management of chronic pain and associated disabilities have coincided with a sharp increase in opioid overprescribing, misuse and abuse.(2, 3) Between 2000 and 2010, opioid prescription rates doubled from 11.3% to 19.6%.(3) Primary care providers account for nearly half of all opioid prescriptions dispensed.(7) The highest rates for prescribing opioids are found in the Appalachian, Western and Southern states like Louisiana which ranks 7th in the nation.(14, 15) The social and mental health sequela of these prescribing trends have reached epidemic proportions. Fatal drug poisonings now exceed the rate of motor vehicle mortalities with overdose mortality rates for prescription opioids surpassing those from cocaine and heroin.(1) In fact, Louisiana is 1 of 19 states with a significant increase in mortality rates from opioid overdoses (12.4%) between 2014 and 2015.(16) Opioid abusers are more likely to utilize medical services at rates exceeding non-abusers for inpatient hospitalizations (12-times higher), emergency department use (4-times higher), and mental health outpatient visits (11-times higher) resulting in increased medical expenditures and loss of productivity costs.(5) *Louisiana, as a major contributor to the epidemic*, has great potential for leading changes in the way we deliver care for patients with chronic non-cancer pain. *We are overdue for implementing safe opioid management strategies in primary care to combat the opioid crisis*.

A.2 Determinants of Opioid Misuse, Abuse and Overdose: Safe opioid management programming requires tackling the complex array of multi-level factors (patient, provider, healthcare system, health policy) that increase risks for misuse, abuse, overdose and mortality. Among *opioid users*, younger age; having a history of prescription diversion or drug substitution; doctor or pharmacy shopping; having a history of psychiatric conditions and use of psychotropic medications are major risk factors for misuse and abuse.(6) *Healthcare provider* opioid prescribing patterns (long-term opioid therapy and higher daily dosage of opioids) further increase patients' risk for abuse, addiction and overdose.(6, 8) Compared to patients prescribed <20 mg morphine equivalent dose (MED) per day, the risk of overdosing is 1.9 to 4.6 times higher among patients prescribed 50 to 100 MED per day and 2 to 8.9 times higher for prescription doses >100 MED per day. A disproportionate share of fatal overdoses is associated with methadone and co-prescriptions with benzodiazepines. (8) Variations in provider opioid prescribing behaviors reflect differences in provider knowledge, attitude and skills for treating chronic pain.(17, 18) Major barriers to effective management of chronic non-cancer pain also include limitations in referral options for pain management or addiction services (*healthcare system*) and on insurance coverage for these services (*health policy)*.(18) Given the complexity of factors contributing to the opioid crisis, *multi-level interventions are likely to be more effective than single component interventions*.

A.3 Clinical Practice Guidelines for Prescribing Opioids for Chronic Non-Cancer Pain: In 2016, the Center for Disease Control (CDC) released *evidence-based practice guidelines* to help providers identify risky opioid user behaviors, heighten provider awareness of prescribing practices and promote use of risk mitigation

strategies. (8) Non-pharmacologic and non-opioid therapy is the preferred treatment option for chronic non-cancer pain. Opioids should only be used when the benefits for pain and function outweigh the risks. Providers should establish realistic treatment goals for pain and function and monitor for recovery**;** prescribe immediate release opioids instead of long acting opioids; prescribe the lowest effective dose; assess benefits and risk of doses >50 MED; and re-evaluate the benefits and harms of opioid therapy every 3 months or more frequently. Providers should also conduct periodic risk assessments and incorporate mitigation strategies into the management plan; review state prescription drug monitoring program data when available; perform urine drug testing at least annually; and avoid co-prescribing benzodiazepines. Finally, patients with opioid use disorder should be referred to evidence-based treatment programs (e.g. Suboxone therapy for addiction). Although the CDC and other guidelines provides recommendations on what to do for safe prescribing of opioids (7-10), *they do not provide guidance on how to translate them into practice at the point of care*.

A.4 Strategies for Promoting Uptake of Clinical Practice Guidelines: Despite the growing number of practice guidelines, provider uptake and adherence can take many years to achieve. The more time it takes to adopt opioid prescribing guidelines, the more lives are lost. *We must find ways to accelerate practice guideline adoption in primary care in the face of an overdose crisis.* Successful implementation of guidelines requires surmounting barriers related to: (1) provider personal factors (e.g. knowledge); (2) guideline factors (e.g. plausibility, accessibility); and (3) external factors (e.g. organizational resources, social/clinical norms).(19) Improving provider awareness/familiarity with practice recommendations while enhancing self-efficacy and motivation is a prerequisite to behavior change. Learning from opinion leaders, being influenced by clinical champions, participating in continuing medical education and receiving feedback on practice performance are effective strategies for influencing changes in provider behavior. Practice guidelines that are evidence-based, plausible, goal-oriented, user-friendly and easily accessed at the point of care are likely to be adopted quickly. Organization level use of computerized decision support systems, reminders and standing orders as well as standardization of processes, procedures and protocols within the context of quality management improves practice adherence. Finally, inter-professional collaborations with other health care professionals facilitates guideline implementation and adherence.

A.5 Integration of Mental/Behavioral Health in Primary Care. Given the high prevalence of major depression with chronic opioid use (11-13), *integration of collaborative mental/behavioral health services may accelerate implementation of safe opioid management in primary care*. Several studies demonstrate that collaborative care is effective for improving management of depression, anxiety and alcohol abuse in primary care.(20) Collaborative care for depressive disorders improves physical and mental health outcomes, quality of life, functional status, satisfaction with care, and provides good economic value with lower cost of care.(21-23) Integration of collaborative care requires routine screening of patients for psychiatric conditions; patient education and self-management support; medication management; clinical monitoring of response to treatment; psychotherapy; standardized follow up; formal stepped care for systematic adjustment of care plans until treatment goals are achieved; and physician supervision.(20) The collaborative care model can *extend opioid management beyond standardized monitoring of risk factors for opioid misuse or abuse and set clear protocols for next steps in management*.

A.6 Gaps in Evidence for Chronic Opioid Management in Primary Care: Health system research that examines a combination *workflow- and provider-focused strategies* to improve primary care physician knowledge, attitude, and skills for managing chronic non-cancer pain and change opioid prescribing behavior are needed (***Knowledge Gap 1***). Primary care practices need feasible ways to monitor opioid safety (adverse effects and toxicities), efficacy (physical and emotional functioning) and misuse throughout the course of treatment without increasing workloads. *Standardized workflow redesigns* employed among practices of

varying sizes, patient mix, and geographic locations would help health care organizations across the country know which interventions work best. However, workflow redesign has limited value if it is not aligned with effective strategies for continuous provider education about why practice changes are needed. More studies examining which *practice-based interventions to continuously educate providers* at the point of care needed (***Knowledge Gap 2***). Health care organizations also desperately need straightforward, patient-centered, sustainable cost effective solutions for implementing safe opioid management programs in primary care. More research is needed on the cost of optimizing technology versus additional care team expansion relative to the benefit of improving the quality of care for patients with chronic non-cancer pain (***Knowledge Gap 3)***.

Our ***main goal*** is to address these knowledge gaps from the perspective of primary care transformation in a complex patient population and provide evidence through a comparative effectiveness and cost effectiveness analysis study. Ochsner Health System, the largest nonprofit, multi-specialty, healthcare delivery system in Louisiana (30 hospitals; 60 health centers; 90 specialties; 600,000 patients; 1.2 million annual clinic visits), is uniquely poised to inform practice redesign to address these gaps and their impact on practice performance with its 36 primary care clinics, Accountable Care Network, Commercial Shared Savings Plans, and Primary Care Research Network. We anticipate that results of our study will allow us to: (1) provide evidence-based strategies for translating opioid management guidelines into practice; (2) identify contextual factors that facilitate/hinder implementation of a multi-component intervention (clinical decision support and care team expansion with a clinical pharmacist and social worker) in diverse practice settings; and (3) demonstrate to health plans that integrated mental/behavioral health care increases value-based care.

B. Innovation

U.S. national health policy is increasingly driving the healthcare industry towards value-based care whereby providers are expected to provide high quality care, improve patient experiences and reduce the cost of care. Associations between mental/behavioral health conditions (including opioid abuse/misuse) and rising healthcare expenditures are well documented. However, few studies *examine the cost-effectiveness of primary care practice transformation strategies* for implementing safe opioid management of chronic non-cancer pain. Limited health plan reimbursements have historically, impeded uptake of behavioral health integration in primary care. Alternative Payment Models under the Medicare Access and CHIP Reauthorization Act of 2015 may ultimately eliminate this barrier; so, it is imperative that healthcare providers have evidence-based tools for tackling the cost-prohibitive opioid crisis. Ochsner's Accountable Care Network, through shared savings plans with Medicare and multiple commercial insurers, is well-positioned to design, implement, evaluate and scale up cost saving interventions.

C. Approach

C.1. Study Overview: This proposal is a 4-year type 2 effectiveness-implementation hybrid stepped wedge cluster randomized control trial to evaluate a multi-component intervention to: (1) increase compliance with the minimum standard of clinical practice as defined by the Center for Disease Control (electronic medical recorded clinical decision support [EMR CDS] guided care); and (2) expand access to additional mental/behavioral health services, medication management and care coordination (stepped opioid collaborative care model [CCM])

Stepped Wedge Cluster Randomized Controlled Trial

Randomization of phased implementation of additional collaborative care model across health system						
Study Months	0-6	7-9	10-12	13-15	16-18	19-21
Region 1	EMR CDS	EMR CDS + stepped opioid CCM				
Region 2	EMR CDS		EMR CDS + stepped opioid CCM			
Region 3	EMR CDS			EMR CDS + stepped opioid CCM		
Region 4	EMR CDS				EMR CDS + stepped opioid CCM	
Region 5	EMR CDS					EMR CDS + stepped opioid CCM

to improve opioid management of primary care patients with chronic non-cancer pain. The stepped wedge cluster RCT design will allow us to examine the clinical impact of the intervention as the two components are implemented in a stepwise fashion across the health system. The EMR CDS guided care component went live across the health system as the standard of practice in October 2017. The stepped opioid CCM component will require 15 months to scale up in 3-month intervals across the health system. We will randomize the order in which stepped opioid CCM becomes available in each region. The study intervention targets *primary care providers (Internal Medicine or Family Medicine)* who are practicing in 35 clinic locations within 5 geographic regions of the Ochsner Health System. We will examine outcomes of care for *their patients who meet the following inclusion criteria* - age 18 and older, have a primary care provider at any of the study clinics, receiving opioid prescriptions (long-acting opioids or >3 months short-acting opioids) for chronic non-cancer pain, and have a diagnosis of depression or anxiety. Patient exclusion criteria include age <18 years, active cancer or undergoing cancer treatment, chronic cancer-related pain, having a terminal illness or receiving hospice care. We must accumulate healthcare data for 578 patients.

In **Aims 1 and 2**, we will compare the *clinical effectiveness* of electronic medical record-based clinical decision support (EMR CDS) versus additional integrated, stepped collaborative care (EMR CDS + stepped opioid CCM) and compare the *cost effectiveness* of the interventions. We hypothesize patients who receive additional stepped opioid CCM compared to EMR CDS guided care only will have greater decreases in total dosage of opioid medication prescribed. We also hypothesize that a higher proportion of patients who receive stepped opioid CCM will receive guideline concordant care, have greater reductions in inpatient hospitalizations and/or emergency department utilization and receive more cost-effective care. **In Aim 3**, we will conduct a qualitative assessment of the *facilitators and barriers* to implementing the multi-component intervention using the Consolidated Framework for Implementation Research. We hypothesize that intervention adaptability to local contexts, clinic readiness for implementation, and physician champions will influence implementation and subsequent performance of the intervention.

C.2. Research Team and Expertise

We have assembled a strong team of investigators with expertise in health services research, patient-centered outcome research, implementation sciences, qualitative research, health information technology optimization, collaborative care management and chronic pain management for the proposed study. We have extensive experience in all areas of relevance to the proposed study. Many of these investigators have collaborated on research projects in the past or are currently collaborating. In addition, Ochsner Health System stakeholders are partners in this research and play a critical role in formulating research questions, designing and monitoring the conduct of the proposed interventions, and helping to plan the dissemination and scale-up of the study findings.

Eboni Price-Haywood, MD, MPH, Principal Investigator, is a General Internist and Director of the Ochsner Health System Center for Applied Health Services Research and Primary Care Research Network. Her research focuses on optimization of health information technology and care teams to enhance population health management, chronic disease care management, transitions of care and health equity. She is Co-PI for the Research Action for Health Network (REACHnet) which is part of the PCORI-funded National Patient-Centered Clinical Research Network (PCORnet). She is also co-investigator for two PCORI-funded studies utilizing the REACHnet infrastructure for the conduct of research in primary care settings.

Lizheng Shi, PhD, Co-Investigator, is a Pharmacist, Professor of Health Economics and Vice Chair in the Department of Global Health Management and Policy, and co-director of the Health Systems Analytics Research Center at Tulane University School of Public Health and Tropical Medicine (Tulane SPHTM). Dr. Shi's research interests focus on health outcomes research and health disparities. He has collaborated with Louisiana Public Health Institute to conduct research on community clinic transformation. He is also a co-

investigator for REACHnet and principal investigator for a study to conduct a natural experiment in primary care examining the uptake and use of the Medicare chronic care management billing codes.

Robert Newlin Jamison, PhD, Consultant, is Professor at Harvard Medical School in the Departments of Anesthesia, Psychiatry, and Physical Medicine and Rehabilitation and has over twenty-five years' experience working with persons with chronic pain. Dr. Jamison is the Chief Psychologist at the Pain Management Center at Brigham and Women's Hospital where he directs a structured pain management program. He has been involved in a number of NIH-funded projects through the National Institute of Drug Abuse. He has developed valid and reliable screening tools to identify individuals with chronic pain who are prone to misuse of prescription opioids. He has also been involved in a large longitudinal study of opioid therapy within primary care.

Lydia Bazzano, MD, PhD, Co-Investigator, is a General Internist, Professor of Epidemiology, Director of the Center for Lifespan Epidemiology Research at Tulane SPHTM and co-chair of the Ochsner Institutional Review Board. She is the principal investigator for the Bogalusa Heart Study, co-investigator for REACHnet and has substantial experience in the design and conduct of both observational studies and randomized controlled trials in community settings.

John Lefante, PhD, Co-Investigator, is Associate Dean for Information Technology and Professor and Chair for the Department of Global Biostatistics and Data Science at Tulane SPHTM. He is also co-director of the Biostatistics and Epidemiology Core for the NIH-funded Louisiana Clinical and Translational Science Center. His research interests include health care quality, access, and evaluation.
Burton Jeffrey, PhD, Co-investigator.

Jeffrey Burton, PhD, Co-Investigator, is Senior Biostatistician for the Center for Outcomes and Health Services Research at Ochsner Health System. He will oversee data management.

Alessandra Bazzano, PhD, Consultant, is Assistant Professor of Global Community Health and Behavioral Sciences at the Tulane SPHTM. She has undertaken qualitative and mixed methods research related to health care accessibility and quality,and collected primary data in this area. She is experienced in a broad range of qualitative study designs and methods.

Alaa Mohammed, MA, Qualitative Data Analyst, is a Junior Biostatistician for the Center for Outcomes and Health Services Research in the Ochsner Health System. She will assist Dr. A. Bazzano with the conduct of qualitative research.

Wanda Robinson, MD, Physician Lead for Opioid Stewardship in Primary Care, is a Family Medicine provider, Chair of Primary Care for the second largest region of Ochsner Health System, and member of the Population Health and Opioid Stewardship Committees. She is the physician champion leading primary care practice redesign to standardize chronic opioid management.

Health system stakeholders include Richard Guthrie, MD (Chief Quality Officer), Todd Burstain, MD (Chief Medical Information Officer), Pedro Cazabon, MD (Primary Care System Chair), Debbie Simonson (Pharmacy System Leader), Jennifer Velander MD (Addiction Psychiatry), Jennifer Archie (Internal Medicine-Psychiatry) and the Ochsner Patient Research Advisory Board.

Jewel Harden-Barrios, MEd, Study Coordinator, Clinical Research Coordinator for the Center for Outcomes and Health Services Research will schedule and implement meeting plans and logistics for the project team, help develop and maintain the manual of procedures and project management plans including project monitoring and reporting, prepare IRB submissions, and oversee and complete recruitment procedures.

Thomas Maestri, Pharm D, Clinical Pharmacist is a member of the Intervention Team. He verifies the inclusion criteria that patients are receiving opioid prescriptions and delivers medication outreach and education for the study program.

C.3. <u>Preliminary Studies</u>

C.3.1. Reducing Health System Opioid Prescription Rates. In 2016, **Dr. Richard Guthrie**, Ochsner's Chief Quality Officer, formed an Opioid Stewardship workgroup to lead local efforts to address the opioid prescription crisis. The workgroup was charged with using data to raise provider awareness of the problem, developing strategies to promote responsible use of opioids for chronic non-cancer pain, and developing infrastructure for opioid treatment and recovery. Review of prescription data demonstrated that among the 348,000 opioid prescriptions written across the system annually, 20% are written in the Emergency Departments. Moreover, among 100 patients identified as Emergency Department super-utilizers (>25 visits in 12-months), 65% were diagnosed with chronic pain. Twenty percent of all ED visits across the system result in opioid prescriptions. The Opioid Stewardship workgroup *piloted a multi-component ED intervention* at one of our hospital facilities that has the second highest opioid prescription rate (26%). Major components of the intervention included adoption of non-opioid pain management practice guidelines, prescribing only low dose immediate release formulations of opioids for short courses (3-5 days), electronic medical record prescription order defaults that lowered dispense quantities, patient education materials and physician peer education targeting behavior modification. Eight months' post-intervention, the overall ED opioid prescription rates dropped 48% but more impressively the provider with the highest prescription rate (35%) had an 80% drop in opioid prescription writing (*Manuscript in Draft*). The model is now being scaled up across our network. Our team's pilot study highlights the role of *centralization* of resources and policies, *standardization* of procedures, provider-patient *education* and *automation* of targeted workflows to influence provider behavior change.

C.3.2 Opioid Management and Mental/Behavioral Health Integration in Primary Care. Reducing practice variation in opioid management among primary care providers is a major priority. Strategies that work in the emergency department may or may not be as effective in primary care settings where providers have continuous relationships with their patients. Our team examined opioid prescription patterns in 36 primary care clinics and confirmed the urgency for integrating structured opioid management strategies in primary care. We conducted a prep-to-research query of prescriptions written within a 120-day period for long-acting opioids or 90-day supplies of short-acting opioids. We identified 2759 patients (1% of the 250,000 primary care patients served) who met our definition of chronic opioid therapy. Approximately 71% of these patients have chronic non-cancer pain, 62% have active diagnoses of depression/anxiety disorders, 56% have Medicare coverage, and 37% are age 65 years and older. We further observed that 6 clinics (located in 5 different geographic regions) each have more than 100 patients receiving chronic opioid therapy in contrast to all other sites.

Dr. Jamison has extensive experience with *implementing structured opioid management* in primary care.(17, 24-30) His body of work includes developing tools to assess patient opioid misuse (Current Opioid Misuse Measure)(30), determine level of risk for substance abuse (Screener and Opioid Assessment for Pain Patients)(29), and adherence to terms of opioid agreements (Opioid Compliance Checklist). (26, 27) His research demonstrates that the combined use of risk assessments, compliance monitoring, specialty support with cognitive behavioral counseling improves patient outcomes.(24) Despite proven effectiveness of this approach to care, physician confidence or comfort with prescribing opioids remains a challenge necessitating ongoing collaborative care for pain management.

Dr. Price-Haywood has substantial experience with implementing *collaborative care management and mental/behavioral health integration in primary care*. (31-35) Her body of work focuses on case identification, risk stratification, chronic disease care management, and stepped care for complex cases. Dr. Price-Haywood's recent work on depression care demonstrated that patients who experienced collaborative mental health care saw their primary care provider (PCP) twice as often, had timelier follow up for monitoring symptoms of depression, and had a higher rate of treatment response, compared to patients who only received care from their PCP.(34) Her research identified facilitators and barriers to implementing these models which include clinic quality improvement leadership; physician education; change management; availability of resources (staff; technology; financing; time); and electronic medical record functionalities that permit case

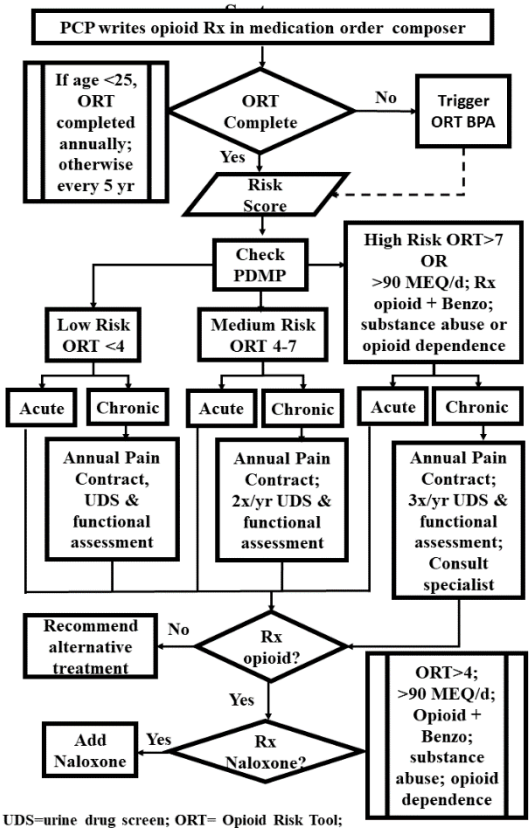
identification and tracking care plans (registry functions); automation of evidence-based practices (clinical decision support) and simplification of workflow (data entry that requires the fewest clicks).(34, 35)

C.3.3. Financing Chronic Care Management. Financing care management for physical and mental health disorders in primary care has historically been challenging; however, recent pay-for-performance health policies that incentivize high value care and shared savings contracts between provider organizations and health plans may generate cost savings that could enable long-term investment in integrated care models. Our research team (**Drs. Shi, Price-Haywood & A. Bazzano**) is currently conducting a 5-year federally funded natural experiment to examine health system uptake, adoption and impact of *Medicare reimbursement* for non-face-to-face chronic care management (CPT 99490) on care coordination in Louisiana.(36) Successes identified thus far include patient perceptions that the most valuable aspect of this service is coordination of multiple specialty appointments; however, *patients desire greater emphasis on care plans and medication management*. Moreover, patient willingness to participate in non-face-to-face care management is hampered by co-pay requirements. Patients question the monetary value of care management via phone. Identifying the right balance between in-person and telephone care management needs further exploration.

C.4. Aim 1: Clinical decision support guided care versus additional collaborative care management

C.4.1. EMR CDS Guided Care for Opioid Management (Usual Care). The EMR CDS is designed to help identify patients who are at risk for opioid misuse/abuse, employ mitigation strategies to prevent progression and refer patients to specialty care in a timely manner in accordance with CDC practice guidelines. Because its *implementation is the result of system level policies and procedures,* the EMR CDS intervention is the *usual care* arm of the study. EMR CDS guided care is based on Epic electronic health record system's Healthy Planet patient registry tool and related population health maintenance workflows that mimic strategies already employed by Ochsner primary care. The health maintenance tool displays whether patients are up-to-date on chronic opioid management best practices. As detailed in Figure 1, providers are prompted to complete the Opioid Risk Tool (ORT) when prescribing opioids if not already documented. The ORT score is used to stratify patients for risk of opioid misuse/abuse.(37) The ORT score, morphine equivalent of the opioid dose prescribed, and hyperlinks to the Louisiana pharmacy drug monitoring program data and current pain management agreement are visible in the medication order composer. Displaying this information in the prescription writer minimizes the number of clicks needed to access the data required for guideline concordant care. An Epic banner appears in the charts of patients with medium to high risk (as per the ORT) to alert other providers of existing opioid management agreements, limit opioid prescription writing, and encourage redirection of patients back to their primary care providers (PCP) for management. Between April to June 2017, EMR workflows were test piloted in one region of the health system and subsequently launched system-wide October 2017.

Figure 1. Opioid Prescribing Workflow in the Electronic Medical Record



UDS=urine drug screen; ORT= Opioid Risk Tool; PDMP=Prescription drug monitoring program; Functional assessment: PHQ4 (Depression/Anxiety Screen); PEG 3-Item Pain Scale

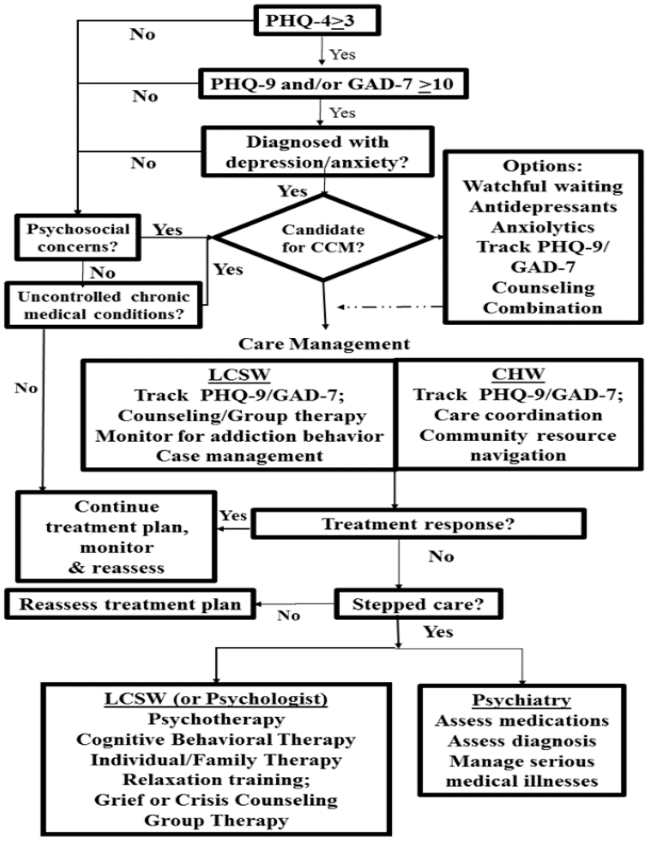
The recommended functional assessment must include at a minimum the PEG 3-Item Pain Scale and depression/anxiety screening (PHQ-4). We selected these questionnaires because they are short and easy to

administer in a busy clinic setting. The **PEG-3** is derived from the Brief Pain Inventory. (38, 39) It has internal reliability and construct validity, and responsiveness among primary care patients. Each item (Pain, Enjoyment, General Activity) is scaled 0-10 with the final score being the average of the 3 individual item scores. The score is best used to track changes in an individual's score over time. A decrease in score over time with the initiation of therapy is considered responsive to treatment. ***PHQ-4*** consists of a two-item measure of depression and two-item measure of anxiety. (40) The scale has internal reliability, construct validity and factorial validity. The score indicates normal (0-2), mild (3-5), moderate (6-8), or severe symptoms (9-12). A score ≥3 on the depression subscale identifies potential cases of depressive disorders while a cut-point of ≥3 on the anxiety scale identifies potential cases of generalized anxiety, panic, social anxiety and posttraumatic stress disorders. Increasing scores are associated with multiple domains of functional impairment and have a strong dose response relationship with disability days and physician visits. The PHQ-4 is not diagnostic and further inquiry to establish the presence of a mental disorder is warranted. If PHQ-4 is ≥3, documentation of **PHQ-9** (41) and **GAD-7** (42-45) is recommended for detailed screening and subsequent monitoring of symptoms should a formal diagnosis be made. Patient responses to questionnaire items are documented via Epic's flowsheet tool to facilitate capturing this information as structured data.

C.4.2. Stepped Care for Opioid Collaborative Care Management (Stepped Opioid CCM). Our preliminary analysis of opioid prescriptions substantiates that most patients receiving chronic opioid therapy in primary care have comorbid psychiatric diagnoses (Section 3.1). *Stepped opioid CCM is an additional component of the overall opioid management strategy* (EMR CDS+ stepped opioid CCM*).* It is designed to systematically expand care options for patients who have comorbid depression, anxiety or psychosocial issues (e.g. problems with relationships, work or school) that may complicate opioid therapy and recovery. Our collaborative care team will be composed of a community health worker (CHW), a licensed clinical social worker (LCSW), and a clinical pharmacist (PharmD). Such personnel are already used across the system, and we will train existing staff in study procedures. As previously described in the Study Design Overview, we will randomize the order in which the service becomes available across 5 geographic regions and initiate service in each region in 3-month intervals over a 15-month period. We will physically locate the service in the 5 clinic locations with the highest opioid prescription rates. However, all clinics within each region can refer patients for care. To control the fidelity of services provided during this study, only CHW-LCSW-PharmD personnel trained in the study protocol will provide stepped opioid CCM.

Figure 2 summarizes our model of care. This intervention is modeled after Dr. Price-Haywood's previous research on integrating mental/behavioral in primary care.(34) Eligibility criteria for stepped opioid CCM include PHQ-9 or GAD-7≥10, clinical diagnosis of depression or anxiety disorder, psychosocial concerns, and chronic pain requiring opioid therapy. We will use the EMR registry and bulk order function to notify providers of eligible patients within their panel. When providers sign off on the referral orders, a list of patients will automatically be generated for clinic personnel to facilitate scheduling baseline assessments.

Figure 2. Collaborative Care Model for Co-Morbid Depression, Anxiety, Psychosocial Disorders and Chronic Non-Cancer Pain



All PCPs will complete online continuing education in population health strategies for managing patients with depression or anxiety. They will be advised that patients with elevated PHQ-9/GAD-7 scores and a diagnosis of depression/anxiety should be re-evaluated in 4-6 week intervals for monitoring and treatment adjustment while symptoms are acute. Treatment plans should be tailored to individual patients. Options include referral to the CHW-LCSW-PharmD team for care management or watchful waiting (1-2 months) with reassessment; antidepressant/anxiolytic medication; referral to behavioral health counseling; or a combination of these approaches. For depression/anxiety care treatment goals, a decrease in PHQ-9/GAD-7 score of five points is considered clinically significant improvement, a decrease in score by 50% is responsive to therapy, and a decrease in score to <5 for three months is considered remission. If PHQ-9/GAD-7 scores indicate non-responsiveness or partial response, then providers are to reassess the diagnosis and contributing factors, modify treatment plans and/or refer to stepped opioid CCM. Regular assessment of ongoing indications for opioid therapy for chronic pain will occur per the EMR CDS protocol.

For patients referred to stepped opioid CCM, all patients will have *baseline in-person, telephonic, or virtual (video) visits* with the CHW and LCSW. All CHW case management and depression/anxiety care management activities will occur under the direct supervision of the LCSW. The ***CHW*** will administer the PHQ-9/GAD-7, **PROMIS-10** and social determinants of health questionnaire at baseline. The PHQ-9/GAD-7 will be administered every 4-6 weeks until symptom scores decrease to <5. The **PROMIS-10** is a standardized measure of health status that provides a single index value that can be use in clinical and economic evaluations of health care. At a minimum, all patients referred to opioid CCM will have the **PROMIS-10** administered during initial assessments and again prior to discharge from stepped opioid CCM. The CHW will update assets and barriers to recovery and self-management (supports; motivation; perceived stigma; co-morbid medical conditions; cognitive problems; side effects; problems with the therapeutic relationship; logistical/economic/ cultural factors); and help patients navigate community resources. Follow-up will occur in-person or via phone as tailored to individual patient needs. CHW assessments will be documented in Epic using standardized care plan templates and reviewed by the LCSW. The follow-up assessment also includes the ***Patient Global Impression of Change (PGIC)*** scale, a 7-item questionnaire that capture's patient's self-reported rating of their overall improvement (i.e. efficacy of treatment).

The ***LCSW*** will conduct depression/anxiety care management under the direction of the PCP. All patients referred to opioid CCM will have the ***Current Opioid Misuse Measure (COMM-9)*** during initial assessments and again prior to discharge from stepped opioid CCM. The COMM-9 is a 9-item questionnaire with a 5-item response scale (0=never; 4=very often) that captures a 30-day period and only includes behaviors that can change over time. Therefore, it can be measured repeatedly. The LCSW will follow up with patients to assess adherence to treatment plans; review symptom progress; review personal goals and help patients problem solve if goals were not met; update assets/barriers/supports to recovery; monitor analgesia (e.g. PEG-3) and monitor for addiction behaviors. The LCSW will provide counseling services as indicated (behavioral activation, psychotherapy, crisis planning, facilitating connection to substance abuse counseling and treatment). Repeat PHQ-9/GAD-7 scores and updated care plans will be flagged for PCP review. The LCSW will also notify PCPs if patients' symptoms are not adequately improved within 10 weeks of starting or changing treatment and include reminders to consider medication change. PCPs will be advised to refer patients to the LCSW (or psychologist if locally available) for psychotherapy and/or psychiatry for consultation regarding psychotropic medication and suspected complicating diagnoses (e.g. bipolar, psychotic, substance abuse, personality disorders). The LCSW will meet once a week with the CHWs and designated psychiatric consultant to discuss complex cases. Care management plans for follow up will be tailored to individual patient needs. All care management will be documented in Epic and sent to PCPs for co-signature.

The ***clinical pharmacist*** will administer all care management remotely. The clinical pharmacist will also review and reconcile active medication lists, including medications in MedMined database; assess medication side effects, drug interactions and adverse events; and re-enforce or revise treatment plans as indicated.

Recommendations for medication adjustments will be sent to PCPs who can then electronically prescribe opioids and other medications directly to the patients' pharmacy via Epic. The follow up frequency will be tailored to individual patient needs depending on the care plan. Pharmacy assessments will occur at a minimum every 12 weeks and will be documented in Epic using standardized care plan templates and sent to PCPs for co-signature.

C.4.3. Physician and Care Team Recruitment and Retention. The EMR CDS intervention is being implemented as part of system level policies for the expected standard of practice for opioid management. Therefore, all employed PCPs will be exposed to this usual care intervention irrespective of this research study. For the stepped opioid CCM arm of the study, only physicians who agree to participate in the study will see the EMR prompt to refer patients. Based on our experience in previous studies, we will employ several approaches to keep PCPs engaged in the study: (1) structured EMR documentation of patient care progress; (2) online continuing medical education; (3) consistent engagement of physician champions and leaders to encourage their peers to participate; and (4) provider meetings to orient staff to the program.
Medical Assistants (MA) are the front-end care team members who are expected to screen for depression and anxiety symptoms with the PHQ4 as part of their rooming standard for Medicare patients and patients on the chronic opioid therapy registry. The study team will submit employee recognitions (Ochsner Value on the Spot) for MAs who most consistently complete the PHQ4.

C.4.4. Patient Recruitment and Retention (Stepped Opioid CCM). All patient care received in the EMR CDS guided care arm of the study is per the discretion of patients' PCPs. Patients in the stepped opioid CCM arm of the study will be recruited by their PCPs who will refer them for care management. Patients may also self-refer by opting-in (i.e., contacting the research staff to express their interest in participating). To introduce the program to potential patients, the research team will send a mailing of the program flyer (i.e. BHI Team Flyer) and/or a MyOchnser notification (see Appendix A. Patient Self-Referral through MyChart). Individuals who receive the flyer or MyOchsner notification must contact the research team for more information. If the patient responds that they are not interested, they will be removed from further contact lists and instructed to let their PCP know if they change their mind about the program services.

All clinical services rendered will be incorporated into routine clinical operations which includes consent to treatment. All services provided by the CHW-LCSW-PharmD team members are grant funded. Therefore, patients will not be charged for services rendered. A variety of approaches will be used to retain patients including offering convenient options of telephonic and virtual visits (e.g. Ochsner Telemedicine MyChart video visits). Based on our experience, we understand the importance of creating a pleasant clinic environment and friendly and welcoming staff presence. We are also very clear from the initial screening session onward about what we expect from patients and what they can expect from us (including co-management and communication of care plans with their PCPs via the EMR). Keeping patients well informed enhances adherence to the intervention.

C.5. <u>Aim 2: Cost Effectiveness of EMR CDS guided care versus additional stepped collaborative care</u>

Regulatory and financial barriers and historical separation of mental/behavioral health and primary care have created systemic barriers to effective behavioral health integration. Separate funding streams for medical and behavioral health discourage PCPs from attempting to address behavioral health issues. Health policy changes under the Medicare Access and CHIP Reauthorization Act of 2015 provides an avenue through which to incentivize behavioral health integration. Alternative Payment Models which reward quality instead of volume of care may incentivize providers through bundled payments that recognize the value of multiple providers in improving patient outcomes. The Ochsner Health Systems' Accountable Care Network is well poised to

provide critical data to health plans and health policy makers on the cost-effectiveness of the proposed multi-component intervention (See *Blue Cross Blue Shield of Louisiana* Letter of Support). One might naturally assume that care team expansion is more expensive than EMR clinical decision support. However, the decreased service utilization may justify the investment long-term. Beyond cost of care comparisons, effectiveness of the proposed intervention on quality of life, productivity, well-being and bodily pain are important considerations. We will, therefore, evaluate clinical effectiveness, cost of care and cost effectiveness of the proposed opioid management programs, using a "piggy-back" economic evaluation approach to analyze data collected during the clinical trial. (47) Refer to Section C.8.2. for details.

C.6. Aim 3: Facilitators and Barriers to Implementing Multicomponent Intervention

We will use the *Consolidated Framework for Implementation Research* to identify factors that facilitate/hinder implementation of and adherence to EMR CDS guided care and stepped opioid CCM.(48) This framework is composed of five major domains and 37 constructs: (1) *intervention characteristic* (e.g. evidence strength and quality; complexity; cost); (2) *outer setting* (e.g. patient needs and resources; external policies and mandates; peer pressure); (3) *inner setting* (e.g. implementation and learning climate; tension for change; leadership engagement; available resources); (4) *characteristics of individuals involved* (e.g. knowledge, beliefs, self-efficacy); and (5) *process of implementation* (e.g. champions; opinion leaders; planning, engaging, executing and evaluating).

We will gather longitudinal qualitative data on the implementation process from meeting minutes, emails and semi-structured interviews collected over the course of this study. The *Opioid Stewardship Workgroup* meets 1-2 times per month. It is composed of physicians from a variety of specialties (primary care, emergency medicine, hospital medicine, and psychiatry), health system stakeholders representing pharmacy, nursing, clinical information systems (Epic analysts), and operations management. All system level opioid stewardship planning, implementation strategy design, data monitoring, and progress evaluation occur at these meetings and related email communications. The *Primary Care Council,* which meets once a month, is a system-wide committee of physician leaders (medical directors) and health administrators engaged in health systems improvement. The group sets the standards for practice transformation, recommend and approve workflow redesigns, and establishes mutually agreed upon clinical performance metrics. The *Patient Research Advisory Board* is a 12-member group of Ochsner patients who meet 4 times per year to advise research investigators on study questions, study design, patient recruitment, data collection, results review and dissemination plans. The patient board will review and advise on barriers to project implementation identified by the opioid stewardship team and primary care leadership; and advise on emerging topics and areas of the project where a more general patient perspective is appropriate. Information gleaned from these meetings will reflect ***health system level factors*** that impact the implementation process. We will also record minutes for *research team meetings* with the CHW-LCSW-PharmD intervention staff and clinic operations leaders who facilitate scaling up the collaborative care management services. These meetings will provide insight to ***practice level factors*** that may influence implementation of the interventions. The study team will conduct semi-structured interviews with program champions and intervention staff. Our plans for thematic content analysis are described in Section C.8.3.

To assess ***provider level factors*** that may contribute to acceptability and adoption of the opioid management protocols, we will administer a 9-item questionnaire to assess provider experience with mental/behavioral health care management interventions.

C.7. Study Variables and Data Collection

We will compare between study groups (EMR CDS guided care vs. EMR CDS+ stepped opioid CCM) the changes in the outcome measures listed in Table 1. The *main study outcomes* are changes in the average daily opioid dose (morphine equivalent dose, MED) and percentage of patients with average daily opioid dose

≥90 MED. *Secondary outcomes* include changes in annual rates of service utilization; process of care measures; patient reported outcomes; and provider reported measures.

C.7.1 EMR and claims data variables: Table 1 describes the data sources and frequency of data collection for each study variable. Most data collected for this study will be derived from Epic electronic health records and claims data. Ochsner Enterprise Data Warehouse (EDW) is a relational database that captures and stores data from Epic and Ochsner's claims data warehouse. A unique identification number is assigned to each patient and it links all data regardless of location within EDW. We have the ability to extract clinical, administrative and medication data (demographics; diagnoses; diagnostic and therapeutic encounters in inpatient, ambulatory, and emergency department settings; procedures, dates of service, provider, facility, laboratory tests performed, referrals to other specialists; financial and other billing codes; medication generic name, pharmacopeia dispensable drug ID, medication strength, medication strength units, medication rote code and description, medication form, dispense quantity, dispense form, dispense units, and medication reconciliation date; medication possession ratio). Quantitative data, compiled from administrative data and claims data, will be assessed for accuracy. Initial internal validity will be established based on a battery of standard tests and aggregate statistics will be examined and pursued should anomalies become evident, particularly when results are compared with known standards. Where feasible, data will be validated against an external source. The study team will review the data regularly, including accrual targets; timeliness and completeness of data collection; and data quality. Quarterly reports on data will be reviewed.

TABLE 1	Outcome Measure	Data Source	Frequency
Main Study Outcomes			
Morphine equivalent daily dose (MEDD)	Average daily opioid dose	EMR & Claims	Quarterly
	% patients prescribed high dose (≥90 MED)	EMR & Claims	Quarterly
	% patients prescribed high dose (≥50 MED)	EMR & Claims	Quarterly
Secondary Outcomes			
Service utilization	Inpatient hospitalization rates	EMR & Claims	Annually
	Emergency department use rates	EMR & Claims	Annually
	Medical and pharmacy costs	EMR & Claims	Annually
Process of care	% Specialty referrals	EMR	Quarterly
	% Pain agreements documented	EMR	Quarterly
	% Urine drug screening documented	EMR	Quarterly
	% Naloxone documented	EMR	Quarterly
	% Non-opioid prescriptions written	EMR	Quarterly
Patient reported outcomes	PEG 3-Item Pain Score	EMR	Quarterly
	Patient Health Questionnaire, PHQ-4 Score	EMR	Quarterly
	PROMIS-10, COMM-9, PGIC	EMR	Quarterly
Physician reported measures	Provider Experience with Mental Health Care Management	Redcap survey	Annually

C.7.2 CHW collected measures and provider survey: The PROMIS-10 and PGIC will be collected using the EMR. Provider surveys will be collected using REDCap, a software toolset and workflow methodology for electronic collection and management of research operational and clinical trial data.(49) This toolset was developed by Vanderbilt University, in collaboration with a consortium of institutional partners. REDCap provides secure, web-based, and flexible applications that provide an intuitive interface for users to enter data and have real time validation rules at the time of entry. These systems offer easy data manipulation with audit trails, ad hoc reporting, and an export mechanism to common statistical packages.

C.7.3 Meeting Minutes and Emails: Meetings minutes and emails will be collected as previously described in Section C.6.

C.7.4 Manual of Procedures (MOP): We will develop an MOP for data collection and will use these standardized approaches in our study. The MOP will describe the procedures for staff training, instructions for maintaining the database, and other operational aspects of the study. All study personnel will be required to participate in a study training session prior to initiating any study procedures. The care management staff (CHW-LCSW-PharmD team) will be trained in intervention protocols (including electronic medical record and Redcap documentation) at baseline and at 1-year intervals throughout the course of the trial. Certification in study procedures will be documented for initial trainings and re-trainings.

C.8. Data Analytic Plans that Correspond to Study Aims

C.8.1. Aim 1 - Anticipated Effect Size, Sample Size Justification, and Analytic Plan.

The primary outcome proposed is the reduction in average daily opioid dose ≥50 mg morphine equivalent dose following enrollment in the EMR CDS + opioid BHI-CCM program. A power analysis was carried out based on the type 2 effectiveness-hybrid clinical trial to determine sample size required to detect a difference in outcome between the intervention and usual care groups.

In a prior study carried out in the Ochsner Health System on the clinical effectiveness of EMR CDS for opioid prescribing, approximately 20% of patients on chronic opioid therapy were observed to have an average daily opioid dose ≥50 MEDD. Using 20% as the expected response rate (RR) for the usual care group, a total sample size of 490 patients - 245 per group - are required to detect a 50% decrease in the BHI-CCM group (RR=10%) with 80% power. The total sample size amounts to an average of 7 patients in each study group within each of the 35 clinics. The sample size estimates are inflated in accordance with the cluster randomized design, incorporating the variance inflation factor $1 + (m - 1)\rho$, where m is the number of clusters (m=35) and ρ is the intra-cluster correlation coefficient ($\rho \leq 0.03$). Accounting for a potential 15% attrition rate, 578 total patients - 289 per group - are needed to attain the target sample size required to detect a 50% decrease in proportion of patients with average daily opioid dose ≥50 MEDD in the BHI-CCM group compared to the usual care group.

At end of study, generalized linear mixed models will be used to assess average daily opioid dose defined as a binary indicator of ≥50 mg morphine equivalent dose and as a continuous measure. The outcomes will be assessed as pre-enrollment to post-enrollment changes in the EMR CDS + opioid BHI-CCM enrolled patients versus those in the usual care setting. Models will incorporate relevant covariates and design effects.

C.8.2. Aim 2 – Cost Effectiveness Analysis

All analyses will follow the guidelines on cost-effectiveness analysis conducted alongside clinical trials and economic modeling.(47) Our primary analysis will be based on the cohort of patients assigned the baseline characteristics of the participants in the proposed trial. Because of the chronic, recurrent nature of opioid

management, we will consider variable time horizon from trial duration to lifetime. We will develop a semi-Markov model to reflect the cycles of health status level of risk reduction (> 50 vs. <=50mg MED), abstinence (discontinuation of opioids), and relapse as well as death among patients treated with opioids. (52) First, we will derive model parameters from the trial data where possible. For example, trial data will provide the transition probabilities and health utility of different health statuses. We will collect information on resource consumptions from electronic medical records which are linked with claims data. Then, we will conduct a literature review for model parameters. In addition, we will project costs and outcomes over the expected duration of treatment and its effects to ensure that all relevant differences in future outcomes of the treatment comparisons will be captured. Specifically, the cost-effectiveness analysis will use the following parameters: 1) Target population–patients on chronic opioids (long-acting or short-acting); 2) Comparators - We will compare costs for clinics with access to both the EMR CDS guided care and CHW-LCSW team versus clinics that only have access to the EMR CDS guided care; 3) Perspectives – Societal, health plans/payers, and health providers (Ochsner Health System); 4) Time horizon - 2 years, 5 years, and 10 years as well as the lifetime ; 5) Outcomes - % reduction in patient prescribed high dose (% <=50mg MED), PEG-3 score, PROMIS-10 quality adjusted life year (QALY); 6) Cost measures - direct medical costs (inpatient, outpatient, pharmacy, lab, etc.) and program costs (material, training, staff unreimbursed time, etc.); 7) Discount rate - 3% (5% as sensitivity analysis); and 8) Results - costs and outcomes will be compared. If one program does not clearly dominate the others (lower costs and better outcomes), then we will calculate incremental cost effectiveness ratios (ICERs) using the EMR CDS guided care program as the base comparator. An incremental cost-effectiveness ratio (ICER) is defined as $\frac{\Delta_c}{\Delta_e}$, and is a comparison of costs and effectiveness between two strategies (S1 and S2), where the estimated components are defined as Δ_c = $Costs_{S1}$ - $Costs_{S2}$, and Δ_e = $Effectivness_{S1}$ - $Effectiveness_{S2}$. The components are point estimates and have an associated uncertainty that is described by 95% confidence intervals. Primary ICER measure will be cost per % reduction below 90mg MED. Secondary measures will be cost per QALY using the PROMIS-10 or PEG-3 score. Non-parametric bootstrapping will be used to estimate parameter uncertainty (ICER 95% CI, CE scatter-plot and CE acceptability curve). Additionally, cost-effectiveness acceptability curves will be used to further interpret the results. A decision to implement the program is based on a threshold willingness-to-pay (WTP). The WTP threshold for a given healthcare system may be $50,000 per QALY for example.(53) Therefore, programs with an ICER below $50,000 per QALY would be desirable. We will evaluate the robustness of results with changes in model inputs, using probabilistic and one-way sensitivity analyses. Probabilistic sensitivity analysis will be executed via Monte Carlo simulation using relevant parameter distributions (e.g., population characteristics in the proposed trial). One-way analysis sensitivity analysis will test key assumptions such as 5% discounting rate, effectiveness of the additional CCM program, and key cost items (rates of inpatient stay, length of stay, and emergency room visits), as well as the WTP threshold of $100,000 per QALY.

C.8.3. Aim 3 – Analysis of Implementation Process. We will employ methodological and analyst triangulation to produce a comprehensive understanding of facilitators/barriers to protocol adherence for chronic opioid management. We will capture data from qualitative and quantitative data sources to permit exploration of complementary and divergent concepts regarding factors influencing protocol adherence that might otherwise not be captured from single sources. Study investigators will use the *Consolidated Framework for Implementation Research* (CFIR) construct coding guidelines and interview guide (http://cfirguide.org/qual.html) for analysis of meeting minutes, emails, interviews, and comments primary care providers share via the provider surveys. See Appendix B. List of Interview Materials The coding guidelines provide definitions for each construct. The non-coded minutes, emails and interview transcripts will be entered into a software package designed to handle unstructured qualitative data. Each year, two trained analysts who are blinded to implementation outcomes will independently code meeting minutes using pre-populated CFIR construct codes. The analysts will then meet to reach consensus regarding differences of opinion about

specific text. Unresolved issues will be brought to the larger research team for guidance and resolution. Study investigators will meet with health system stakeholders to review examples of coded statements to make sure they accurately capture diverse perspectives of patients, clinicians, administrators, and health system leaders. We will quantify the frequency with which CFIR constructs are coded. We will then organize the data according to the implementation phase during which the data was collected (pre-implementation [before phasing in collaborative care] vs. post-implementation). We will further classify the data as system-, practice-, provider-, or patient-level factors that facilitate or impede implementation of the multicomponent intervention.

D. Project Timeline

The Principal Investigator will oversee and monitor progress to reach the milestones with decisions concerning short-term goals and the evaluation of longer-term progress being discussed with research staff via weekly meetings. Broader management of the project will be undertaken by a Project Management Committee, comprised of the Principal Investigator, selected co-investigators, and 3 health system stakeholders. The Principal Investigator will adjust as needed the approach used to achieve the milestones. Any Unexpected difficulties will be worked out at one of these forums. Table 3 illustrates study activities. By the time funding for this proposal begins, the usual care intervention (EMR CDS guided care) will have been in progress for about 1 year. During the first six months, we will develop data queries and validate reports; design our database; and recruit and train intervention staff. We plan to pilot the stepped opioid CCM intervention by month 7. We are confident we can scale up the intervention in 15 months given the extensive experience of the investigators and health system leadership, availability of trained staff and reliance on the research infrastructure of Ochsner, Tulane University and the Louisiana Clinical and Translational Science Center. We will be able to collect data for 24 months of the multi-component intervention across all study sites. Measurements will end year 4 quarter 2 leaving six months for completion of data analysis and writing papers.

TABLE 3 PROJECT ACTIVITIES & MILESTONES	Year 1				Year 2				Year 3				Year 4			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Assemble and orient research team		X														
Finalize data elements		X	X													
Design database and Redcap survey		X	X													
Develop MOP		X	X													
IRB approval		X														
Trial registered at clinicaltrials.gov			X													
Develop EMR/claims data queries & validate reports		X	X													
Run reports, clean and analyze EMR/claims data			X				X				X				X	
Develop EMR care management templates		X	X													
Conduct CHW-LCSW-PharmD staff training			X			X				X				X		
Implement CHW-LCSW-PharmD care management				X	X	X	X	X	X	X	X	X	X	X	X	X
Administer & analyze provider survey			X				X				X				X	
Opioid Stewardship/Primary Care/Patient Board meetings (Collect/record minutes)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Analyze meeting minutes			X				X				X				X	
Publications and results dissemination				X				X				X				X

PROTECTION OF HUMAN SUBJECTS

The proposed study will be conducted in compliance with all federal and state regulations for protecting human research participants. All research involving human subjects is reviewed by the Ochsner Health System Institutional Review Board prior to implementation for participant protection. Institutional Review Board (IRB) approval for the proposed study is expected within the first quarter of the grant period.

Per federal regulations, we are responsible for assuring that “all activities related to human subjects, regardless of funding source, will be guided by the ethical principles in the Belmont Report.” To do this, all study team members will participate in a human subjects protection education program. Many of them have already done so. Completing a Collaborative Training Initiative (CITI) online course in human subjects protection will be required for those who have not already received such training. Ethical issues (e.g. confidentiality, vulnerable subjects) are discussed in each module of the CITI course. The course includes graded post-tests requiring a minimum score to receive a completion certificate.

Risks to Human Subjects

Human Subjects Involvement, Characteristics and Design. The proposed study is designed to compare the effectiveness of two practice-based interventions to improve opioid management. It employs principles of adult learning theory whereby education occurs during the course of routine practice via electronic medical record clinical decision support and care team support to guide therapeutic management decisions. The study includes three Specific Aims. For **Aim 1**, we will conduct a comparative effectiveness analysis of the study interventions. The study subjects will include primary care physicians (N=176) and their patients with chronic non-cancer pain on opioid therapy (N=578) from 35 primary care clinics. For **Aim 2**, we will conduct a cost effectiveness analysis of the study interventions implemented in Aim 1. For **Aim 3**, we will conduct a qualitative analysis to examine the facilitators and barriers to implementing the study interventions in Aim 1.

Sources of Materials.
For **Aims 1 and 2**, we will collect clinical and claims data to measure the main study outcomes (average morphine equivalent dose opioid prescriptions); and secondary outcomes (annual rates of service utilization; process of care measures; patient reported outcomes). . Specifically, Ochsner Information Analysts will export electronic medical records and claims data from the Enterprise Data Warehouse on a quarterly basis throughout the course of this study. Opioid prescription information from MedMined will be used as a data source. The analysts will upload data files onto a HIPAA-secure web-based file server**.** At the end of each study year, we will also administer a survey to assess changes in primary care physicians' attitudes and satisfaction with opioid management programming. **For Aim 3**, we will collect meeting minutes, emails, and conduct semi-structured interviews throughout the course of this study and comments physicians share via the annual survey.

***Potential Risks*.** The risks for physical, psychological, social or legal harm are minimal from the present study. Specifically, we believe that the probability and magnitude of physical or psychological harm from enrollment in the present study is no more than that which is normally encountered in the daily lives of participants, or in the routine medical, dental, or psychological examination of healthy persons (45 CFR 46.303(d)).The primary risk for patients, staff, and providers participating in this study is the potential for having confidential information exposed, which will be minimized by following strict procedures as outlined below and by following any additional requirements as directed by the Ochsner IRB members.

Adequacy of Protection against Risks

Recruitment and Informed Consent.

We plan to request a waiver of **consent for participation in opioid management** and waiver of HIPAA authorization for extraction of clinical data from the enterprise warehouse.

For the **semi-structured interviews**, we are requesting a waiver of documentation of consent and will obtain verbal consent from interviewees volunteering to participate. The verbal consent to interview template is attached.

For the **online provider survey**, we also are requesting a waiver of documentation of consent. There will be a consent statement as follows: *By electronically submitting the survey, you are providing consent to participate. You are free to decline to answer any question you do not wish to answer.*

We believe the proposed study meets the four requirements of 45 CFR 46.116(d) for waiver of consent: (1) the research involves no more than minimal risk to the participants; (2) the waiver or alteration will not adversely affect the rights and welfare of the participants; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the participants will be provided with additional pertinent information after participation. Should the Ochsner IRB find otherwise, we will abide by the IRB determination.

Protections Against Risk. Data extracted from the Enterprise Data Warehouse (average morphine equivalent dose, opioid prescriptions, annual rates of service utilization, process of care measures, patient reported outcomes) will be stored on HIPAA-secure file servers.xAs outlined below, a Code Book or cross table of participant ID codes and identifying information will be stored securely and separately from the actual data so that the information collected is kept confidential. Data files will not be labeled with identifiable information for participating individuals. In addition, risks will be minimized by maintaining confidential records of all data gathered from the organizational surveys and interviews. Transcripts will be redacted wherever specific names are used or references are made that could identify individuals (for example geographical locations).

General Approach: The research team will take appropriate steps to preserve the confidentiality of the information on research subjects. A Manual of Operations Procedures will be developed and will include procedures for data collection and staff training and instructions for using all project databases. Information collected during the project will be kept confidential, and scientific publications will present data in such a way that it is not possible to determine the identity of individual participants. All records will be kept in locked areas by assigned study number. All computerized data will be password protected. For tracking purposes, a Code Book will contain the name; email address; telephone numbers; MRN; and randomly generated Study ID of potential participants. The Code Book will be password-protected and accessible to the PI and designated team members Price-Haywood and Harden-Barrios. Any email sharing of password-protected files will be encrypted according to Ochsner IT procedures. All electronic study data will be kept in password protected databases. Any paper records will be kept in the Research Department on Ochsner Main Campus in the Academic Building.

Online Survey Data Collection: The study team will make clear to all providers completing the online surveys that participation is voluntary and that they can withdraw from the study if their initial or ongoing experience makes it oppressive, burdensome, or otherwise uncomfortable. Study data will be collected and managed using RedCap electronic data capture tools hosted at Ochsner Health System. All survey data collected will be stored securely using the research software RedCap. It was developed specifically around HIPAA-Security guidelines and has been disseminated for local use at more than 270 other academic/non-profit consortium partners on six continents. RedCap provides secure, web-based flexible applications that provide an intuitive interface for users to enter data and have real time validation rules, with automated data type and range checks, at the time of entry. These systems offer easy data manipulation with audit trails, ad hoc reporting, and an automated export mechanism to common statistical packages. Other security features of RedCap include secure remote login, audits of remote access login, and encryption of data at rest and in transit using Secure Sockets Layer encryption.

Project Databases: Designated research team members will have user access to RedCap and project databases for the purpose of the study. The underlying database is hosted at the Ochsner Information Systems Department that has state-of-the-art security, environmental controls, and backup power. Operating system security includes: secure remote login, audits of remote access login, and encryption of data at rest and in transit using Secure Sockets Layer (SSL) encryption. Copies of data are replicated nightly to a secure

off-site recovery data center. There are 30+ point-in-time copies of data available at any time. Disaster recovery to the remote recovery data center has been tested.

Once the data collection ends, the inactive project or survey (i.e. that is not collecting data) can be archived easily on RedCap. The survey data will be kept on RedCap and on department computers, in a secure manner, at least three years after completing the research activities in order to be available for inspection by authorized agencies. Records stored on a computer hard drive will be erased using commercial software applications designed to remove all data from the storage device. Investigators will delete the project stored on RedCap. Deleting a RedCap project completely, and permanently, removes all the information associated with that project. More specifically, deleting a project will 1) delete all the forms in the project; 2) remove all the associated project data; and 3) delete the project database

Potential Benefits of the Proposed Research to Human Subjects and Others

There may be no direct benefits to subjects for participating in this research, but the knowledge gained from the study may: (1) inform the design of practice-based strategies to change provider attitude, knowledge, skills and behavior regarding opioid management; (2) guide health plans in determining how best to support reimbursement for care team expansion and optimization for population health management, care management and care coordination to improve quality and reduce cost of care.

Importance of the Knowledge to be Gained

This study will examine implementation of structured opioid management programming in “real-world” diverse clinical settings to educate providers on current practice standards. Outcomes to be examined were selected by relevant stakeholders. Members of the study team will further engage stakeholders in assessing the benefits and value of study findings to improve the health delivery system while optimizing outcomes of interests to patients, their caregivers, provider organizations, and health plans.

DATA AND SAFETY MONITORING PLAN

I. Overall Framework for Safety Monitoring

Overview – The primary aim of this study is to test the comparative effectiveness of a patient-centered, pragmatic, scalable, multicomponent opioid management program delivered within primary care as compared to electronic medical record (EMR)-based clinical decision support (EMR CDS) guided care. The study procedures pose little to no risk for human subjects. Specifically, we believe that the probability and magnitude of physical or psychological harm from the present study is no more than that which is normally encountered in the daily lives of participants, or in the routine medical, dental, or psychological examination of healthy persons (45 CFR 46.303(d)).

Framework for Safety Monitoring – The data collected in this study is entered into the EMR as well as REDCap study databases. The study procedures include collecting the following questionnaires which will be administered by the primary care team as part of their usual care practices: (1) Depression and Anxiety Screening; and (2) PEG 3-Item Pain Scale. The ten-item Patient-Reported Outcomes Measurement Information System (PROMIS 10), nine-item Current Opioid Misuse measure, and the seven-item Patient Global Impression of Change will only be collected from patients who consent to receiving collaborative care

management upon referral to the program by their primary care physician. Responses to these questionnaires will be monitored such that high scores indicating moderate or severe depression (for example on the PHQ-9) or suicidal/homicidal ideation (PHQ-9), will automatically trigger alerts to the study team and primary care physician via the EMR. Study personnel and staff will take appropriate measures to ensure patient safety and follow-up are arranged. In addition, all participants seeing a behavioral care professional will be provided with contact information for crisis intervention counselors. If substance addiction or abuse is identified via the addiction behavior checklist, alerts to the study team and primary care provider will be triggered. Participants will be referred to the addiction behavior unit at Ochsner. Study personnel and staff will ensure that appropriate follow up care is provided.

A. Expected Risks –The primary risk associated with this is breach of confidentiality.

B. Adherence Statement - The Data Safety Monitoring Plan (DSMP) outlined below will adhere to the protocol approved by the Ochsner IRB.

II. Confidentiality

A. Protection of Subject Privacy – All volunteers are assured of their confidentiality both verbally and in writing (e.g. electronic statements placed before survey questions). Confidentiality will be ensured by use of identification codes. Volunteers' medical records are electronically stored according to ID numbers. The facilities are strictly limited to the staff of the research institution, clinics and to research volunteers. This is accomplished by a variety of stringent security measures. All medical records are stored in locked areas or electronically in the health system's electronic health record Access to these areas is limited to the clinical support staff and the PI of the study.

B. Database Protection – Electronic data storage is similarly restricted with only the data management staff having access to databases containing confidential clinical records, i.e. those containing name or other identifying information.

III. Data Quality and Safety Review Plan and Monitoring

A. Per the Ochsner Institutional Review Board, this minimal risk study does not require a formal Data Safety and Monitoring Board. This decision was approved by the program officer for the study's sponsor National Institute on Drug Abuse.

The study's team of investigators will meet regularly throughout the study period. A minimum of 1 meeting each year will be conducted in person, other meetings may be conducted via conference call.

A2. Major Responsibilities:

1- Sign and abide by a statement of confidentiality
2- Disclose any actual or potential conflicts of interest
3- Be familiar with research protocol and plans for safety monitoring
4- Oversee safety of participants to include review of adverse events(e.g. hospital/emaergency department admissions, deaths
5- Review reports of related studies, as appropriate
6- Review major proposed modifications

A3. Reports. Following each meeting, the study team will provide written documentation regarding findings for the study as a whole, and any relevant recommendations related to continuing, changing, or terminating the study. All investigator recommendations will be submitted to the Principal Investigator and/or his designee, with a copy provided to the Ochsner IRB and NIDA Project Officer or designee.

The study investigators will monitor and review recruitment, data quality, outcome data, and overall performance. The PI and project manager will regularly review all data collection forms and source documents on an ongoing basis for data completeness, accuracy, and compliance with the protocol and Standard Operating Procedures (SOPs) of Ochsner Health System. A statement reflecting the results of the review and describing any protocol deviations will be sent to the Ochsner IRB in an annual report (non-competing continuation).

B. Subject Accrual and Compliance - Review of subject accrual, adherence to inclusion/exclusion criteria, and rates of study completion will occur quarterly. These data will be reviewed by the study PI and presented during regular investigator meetings.

C. Stopping Rules - This study will be stopped prior to its completion if: (1) adverse effects that significantly impact the risk-benefit ratio have been observed; (2) study recruitment or retention becomes futile; (3) any new information becomes available during the trial that necessitates stopping the trial; and (5) other situations occur that might warrant stopping the trial. Dr. Jennifer Archie, MD, Ochsner Primary Care and Outpatient Psychiatry, serves as the CCM consulting Psychiatrist and has been designated to review adverse events and determine their relatedness to treatment, severity, seriousness, etc.
Because one of the most likely reasons for stopping the trial is the inability to recruit the study sample, the PI will include an assessment of recruitment futility in the annual progress report to NIDA and will consult with a biostatistician if necessary to assess the impact of significant data loss due to problems in recruitment, retention or data collection.

D. Justification of Sample Size - Using 20% as the expected response rate (RR) for the usual care group, a total sample size of 490 patients - 245 per group - are required to detect a 50% decrease in the BHI-CCM group (RR=10%) with 80% power. The total sample size amounts to an average of 7 patients in each study group within each of the 35 clinics. The sample size estimates are inflated in accordance with the cluster randomized design, incorporating the variance inflation factor $1 + (m - 1)\rho$, where m is the number of clusters ($m=35$) and ρ is the intra-cluster correlation coefficient ($\rho \leq 0.03$). Accounting for a potential 15% attrition rate, 578 total patients - 289 per group - are needed to attain the target sample size required to detect a 50% decrease in proportion of patients with average daily opioid dose $\geq$50 MEDD in the BHI-CCM group compared to the usual care group.

E. Safety Review Plan - The PI will monitor the progress of the study weekly, including reasons for attrition and whether all participants met entry criteria. Further, progress and safety will be reviewed quarterly. These progress reports will include information on recruitment, retention/attrition, and AEs and will be provided to the study investigators quarterly. The Ochsner IRB will receive a yearly report that details data relevant to the possible early termination of the study.

VI. Informed Consent: We request a waiver of consent and waiver of documentation of consent based on the requirements at 45 CFR 46.116(d).

APPENDICES

Appendix A. Patient Self-Referral through MyChart

Study teams may send recruitment notifications to potentially eligible patients via the MyOchsner patient portal. The patient-facing recruitment messages must be reviewed and approved by the IRB and then submitted in an Epic Enhancement request. The request will include the following patient-facing study name and description in Table 1.

Table 1 MyChart Recruitment Notification

Collaborative Care for Primary Care Patients with Chronic Non-Cancer Pain

Description: Description: We are studying whether collaborative care will have a positive result on the physical, mental, and social well-being of patients living with chronic pain. Collaborative care means that your Primary Care team includes additional Behavioral Health Care professionals working together to support your care plan. The Behavioral Health Care team member's services (e.g. care coordination, counseling, medication management) are free for a limited time. To make services easier to use, you may meet with your behavioral health care team by telephone or virtual visits through MyOchsner.

We would like to speak with you to determine if you are eligible**.** If you are, we will follow-up with your Ochsner primary care provider to refer you to participate.

This study is funded by the National Institute of Health, grant number 1 R01 DA045029-0. This message has been approved by the Ochsner Institutional Review Board, Protocol # 2018.294

Name | Title | Ochsner Center for Outcomes and Health Services Research | Phone: 504-842-8604

Once the request is approved, the study team builds a report based on patient eligibility in Epic Reporting Workbench or other Epic platform recommended by Ochsner IS The report criteria may include:

- Age in years: greater or equal to 18
- Study: (Display)
- Enrollment Status Type: (Display this column, so we don't sent to someone already screened)
- Mychart status: Active
- Patient Status: Not equal to Deceased
- Most recent questionnaire answers (PHQ4): (Display if available, as to not repeat screenings completed within the last month)
- Diagnosis: exclude serious mental illness

The generated report can be used to “Send Recruitment Request” to patients on the report. The Recruitment Studies Notice shown below in Figure 1, shows up on the homepage of the patient’s MyOchsner account.

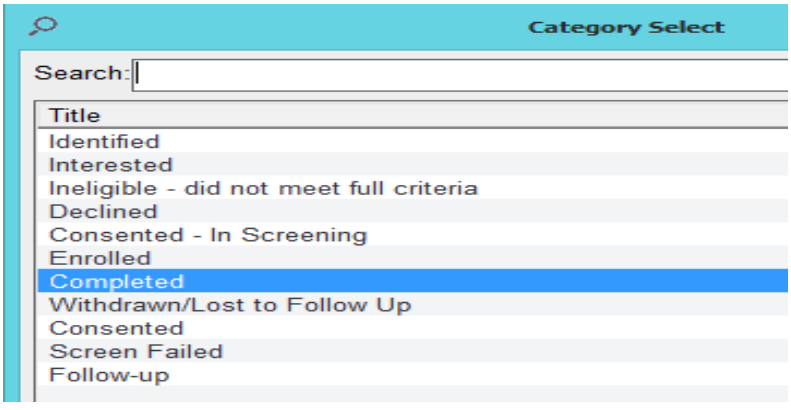
Figure 1 Recruitment Studies Notice

Patients or proxy account users (family/friends/caregivers) may click on the notice to be taken to the Research Studies/Available Studies page to review the study’s recruitment message. Patients will be able to select “I’m Interested” or “No Thank You” to whether they would like to notify the study team that they may want to participate. The responses, both positive and negative, are populated in the study coordinator and principal investigator’s Epic InBasket, in the system’s pre-labeled ***Research Recruitment*** folder.

Interested Patients Workflow

1. The study coordinator will review the Research Recruitment folder for patients with “**Completed”** enrollment status. “Completed” is the default enrollment status based on the recruitment notice being read and ***“I’m Interested”*** being selected by the patient. **If the patient has not responded to the notice**, the default enrollment status is **“Identified”.** Figure 2 is an image of the of Enrollment Status Categories in Epic.

Figure 2 Epic Enrollment Status Categories



2. The CHW or study team member will conduct a **brief chart review** to look for anything in the chart that would deter or defer patients from following up (e.g. admission, prolonged/terminal illness).
3. If no concerns, or red flags, the CHW or study team members (i.e. only Ochsner employees or Ochsner medical students) will call the patient to explain the program and invite them to complete the screening assessment with the PHQ9 and GAD7. If the patient screens eligible and is agreeable, the CHW or study team member will complete the intake procedures (PROMIS and scheduling appointment with the LCSW). Patients may have the option to

complete screening and/or intake by phone or if available, in-person (e.g. upcoming clinic appointment).

4. When **the study team/CHW-administered PHQ9/GAD7 score meets the threshold (either score >=10**), the PCP will be notified of their patient's program eligibility or ineligibility and will be given instructions on how to place the referral mentioned above.

Screening Log

The study team will add all patients screened for eligibility to the Research Study activity in Epic and document the screening date (i.e. start date), the recruiter name (i.e. CHW), the reason for ineligibility or decline, and enrollment status (e.g. enrolled, screen failed, ineligible-did not meet full criteria, declined).

Appendix B. List of Interview Materials

(Documents submitted for review)

1. Ochsner NIDA Draft CFIR Interview Guide_Phase 1 CDS Implementation.9.28.19
2. Phase 1 EMR CDS handout for Interviewee
3. Ochsner NIDA Draft CFIR Interview Guide_Phase 1 Opioid Stewardship Programming.9.28.19
4. Phase 1 Opioid Stewardship handout for Interviewee
5. Verbal Consent to Interview Template
6. Interview Guides: Intervention Team; Referring Primary Care Physicians; Intervention Team

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